surprising as nanoparticulate compositions are designed for immediate, fast release. Such fast release is a result of the nanoparticulate size of the drug, having a large surface area in relation to the volume, which results in rapid dissolution of the drug following administration. However, rapid dissolution is contrary to the goal of controlled release formulations.

Applicants unexpectedly discovered that nanoparticulate compositions could effectively be formulated into controlled release formulations. This is not shown or suggested by the cited prior art.

III. THE OFFICE ACTION

Claims 1-22 and 25-35 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Patent No. 5,145,684 ("Liversidge et al.") and maintained in the Advisory Action of September 25, 2001. Applicants respectfully traverse this ground of rejection.

A. Summary of Liversidge et al.

Applicants' claimed invention is an improvement over commonly-owned Liversidge et al., which is the first patent to disclose nanoparticulate drug compositions. *See* page 5, lines 25-27, of the application. Liversidge et al. teach nanoparticulate compositions comprising active agents and surface stabilizers. This reference does not teach incorporation of such nanoparticulate compositions into a controlled release dosage form, as discussed below.

B. The Examiner's Basis for the Rejection of the Claims over Liversidge et al.

In support of the rejection, the Examiner stated that Liversidge et al. teach nanoparticulate compositions, excipients for such compositions, and solid dose forms of such compositions. The Examiner asserted that Liversidge et al. teach incorporating the nanoparticles with known rate controlling polymers and that this incorporation would provide controlled release properties. The Examiner then concluded in the Final Office Action that "[o]ne of ordinary skill in the art would have been motivated to produce a well known pharmaceutical dosage form, such as a tablet,

which incorporates Liversidge's nanoparticles, and the necessary excipients, especially based on Liversidge's disclosure that his particles are intended for this exact purpose." Applicants respectfully disagree with the Examiner's analysis and conclusion.

C. Liversidge et al. Do Not Teach or Suggest Nanoparticulate Controlled Release Formulations

As previously pointed out in the response filed on September 12, 2001, Liversidge et al. fail to describe a solid dosage form which exhibits the ability to release an active agent over a long period of time. In fact, Liversidge et al. teach away from the present invention because the patent specifically teaches that "the rate of dissolution of a particulate drug can increase with increasing surface area, *i.e.*, decreasing particle size." *See* col. 1, lines 28-30, of U.S. Patent No. 5,145,684. This means that the invention of Liversidge et al. was directed to a drug formulation which allows for rapid dissolution and, therefore, rapid onset of the effect of the drug. This is inapposite to the present claims.

The application of a surface modifier is believed to act to prevent flocculation and agglomeration of the particles by functioning as a mechanical or steric barrier between the particles, minimizing the close, interparticle approach necessary for agglomeration and flocculation. *See* col. 8, lines 21-27, of U.S. Patent No. 5,145,684. There is no discussion in Liversidge et al. that teaches or suggests that a surface modifier could be used to prepare a controlled release nanoparticulate solid drug dosage form.

Moreover, the Examiner appears to be of the opinion that the surface modifier can act as a rate controlling polymer. However, the present claims recite not only the poorly soluble nanoparticulate drug and the surface modifier, but also a pharmaceutically acceptable rate-controlling polymer. Liversidge et al. fails to teach or suggest such a combination.

Thus, formulation of nanoparticulate compositions into the solid dose forms of Liversidge et al. fails to teach or suggest a nanoparticulate formulation of a solid dose *controlled release* dosage form, as recited in the present claims.

As stated in the response filed on September 12, 2001, Chang et al. recognize the difficulty in preparing sustained release drug dosage forms. Chang et al. state that "[d]esign of a sustained-release product is normally a very difficult task . . ." Chang et al. at 201. In addition, this reference teaches that drugs with low water solubility, which are encompassed by Applicants' claims, are "difficult to incorporate into a sustained-release mechanism." Chang et al. at 206. This normally difficult task is complicated in the case of the present invention, in which the active agent is in the form of nanoparticles which are designed for *fast* and *immediate* release. This is exactly the type of evidence that rebuts a holding of prima facie obviousness. As stated in MPEP § 2141,

> [o]bjective evidence or secondary considerations such as unexpected results, commercial success, long-felt need, failure by others, licensing, and skepticism of experts are relevant to the issue of obviousness and must be considered in every case in which they are present. When evidence of any of these secondary considerations is submitted, the examiner must evaluate the evidence.

The discussion in Chang et al. demonstrates the difficulty those practicing in the relevant art have experienced in formulating controlled release drug dosage forms. Furthermore, the Court of Appeals for the Federal Circuit has stated, "evidence rising out of the so-called 'secondary considerations' must always, when present, be considered en route to a determination of obviousness." *Stratoflex, Inc.v. Aeroquip Corp.*, 713 F.2d 1530, 1538, 218 U.S.P.Q. 871, 879 (Fed. Cir. 1983). Therefore, the Examiner is respectfully requested to review the objective evidence submitted with the previous reply filed on September 12, 2001, as evidence of unobviousness.

For at least these reasons, Liversidge et al. fail to teach or suggest the claimed invention and, therefore, reconsideration and withdrawal of this ground for rejection are respectfully requested.

IV. CONCLUSION

Applicants courteously request reconsideration of this application in view of the above remarks. This application is now in condition for allowance and early notice to that effect is respectfully solicited.

If there are any fees due in connection with the filing of this Amendment, please charge the fees to our Deposit Account No. 19-0741. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Dated: Dec. 3, 2001

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